EXHIBIT 1

LEXSEE 2002 US DIST LEXIS 4659

ABBOTT LABORATORIES, an Illinois corporation; FOURNIER INDUSTRIE ET SANTE, a French corporation; and LABORATOIRES FOURNIER S.A., a French corporation, Plaintiffs, v. NOVOPHARM LIMITED, a corporation of the dominion of Canada; and TEVA PHARMACEUTICAL INDUSTRIES LTD., an Israeli corporation, Defendants.

Nos. 00 C 2141, 00 C 5094, and 01 C 1914

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ILLINOIS, EASTERN DIVISION

2002 U.S. Dist. LEXIS 4659

March 19, 2002, Decided
March 20, 2002, Docketed

SUBSEQUENT HISTORY: *Affirmed by Abbott Labs v Novopharm Ltd, 2003 U.S. App. LEXIS 5357* (Fed. Cir., Mar. 20, 2003)

DISPOSITION: [*1] Defendant Novopharm's motion for summary judgment of noninfringement was granted.

LexisNexis(R) Headnotes

COUNSEL: For FOURNIER INDUSTRIE ET SANTE, LABORATORIES FOURNIER S.A., plaintiffs (00-CV-5094): Charles D. Ossola, Arnold & Porter, Washington, DC.

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For ABBOTT LAB, plaintiff (00-CV-5094): Daniel E. Reidy, James A. White, Tina M. Tabacchi, Timothy John Heverin, Jones, Day, Reavis & Pogue, Chicago, IL.

For NOVOPHARM LIMITED, defendant (00-CV-5094): Bruce Michael Gagala, Robert F. Green, Marion D. Hefner, Leydig, Voit & Mayer, Ltd., Chicago, IL.

For NOVOPHARM LIMITED, counter-claimant (00-CV-5094): Bruce Michael Gagala, Robert F. Green, Marion D. Hefner, Leydig, Voit & Mayer, Ltd., Chicago, IL.

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For ABBOTT LAB, counter-defendant (00-CV-5094): Daniel E. Reidy, James A. White, Tina M. Tabacchi, Timothy John Heverin, Jones, Day, Reavis & Pogue, Chicago, IL.

JUDGES: JOHN W. DARRAH, United States District Judge.

OPINIONBY: JOHN W. DARRAH

OPINION:

MEMORANDUM OPINION AND ORDER

Defendant, Novopharm, filed an Abbreviated New Drug Application ("ANDA") seeking the Food and Drug Administration's ("FDA") approval to market a generic micronized fenofibrate product in three dosage forms.

Subsequently, Fournier, the owner of the Curtet Patent, and Abbott, Fournier's exclusive licensee under the Curtet Patent, filed the present actions for each of Novopharm's three proposed dosage forms, alleging that the process described in Novopharm's ANDA and the products produced by that process would infringe the Curtet Patent. The three lawsuits were consolidated. Presently before the Court is Novopharm's Motion for Summary Judgment of Noninfringement. **[*3]**

FACTS

The Curtet Patent has 12 claims. (Def.'s 56.1(a)(3) Statement P 20). Claims 1 and 10 are the only independent claims of the Curtet Patent. Claims 2-9 and 11-12 depend ultimately from claim 1. (Id., at PP 21-22).

Claim 1 of the Curtet Patent, as originally filed, stated:

> A therapeutic composition, presented in the form of gelatin capsules, which is useful especially in the oral treatment of hyperlipidemia and hypercholesterolemia, the said composition containing fenofibrate and a solid surfactant which have been co-micronized. (Def.'s 56.1(a)(3) Statement P 75)

During the Patent's prosecution, the United States Patent and Trademark Office ("PTO") issued an "Office Action", rejecting claim 1 under *35 U.S.C. § 103* as being obvious over Schonafinger *et al.* in view of Schonafinger and Grouiller. (Id, at PP 76-77).

In July 1989, Fournier submitted an amendment in response to the Office Action. The amendment added the present limitation of "a co-micronized mixture of particles". (Id., at PP 78-79).

Fournier distinguished the cited prior art from the claimed invention, as amended, on the ground that the prior art did not teach **[*4]** or suggest co-micronization of fenofibrate and a solid surfactant such that co-micronization as claimed resulted in an improvement, namely improved bioavailability. (Def.'s 56.1(a)(3) Statement P 82) In response to the Office Action, Fournier explained to the PTO that "none of the [cited] references alone in any combination thereof teaches or suggests co-micronization of a mixture of fenofibrate and a solid surfactant." (Id., at P 83). Fournier also explained that "none of the [cited] references alone or in any combination thereof teaches or suggests ... that by co-micronizing said mixture a lower daily dosage may be administered because the bioavailability of fenofibrate is significantly and unexpectedly increased." (Id., at P 84).

The amendment also stated that "Groullier et al [does not] teach or suggest co-micronization of a mixture of fenofibrate with a solid surfactant to produce particles having a diameter of less than 15 [mu] m." (Def.'s 56.1(a)(3) Statement P 85). It further differentiated Schonafinger, stating that "Schonafinger ('743), thus, does not teach or suggest co-micronization of fenofibrate with a solid surfactant." (Id., at P 86). Fournier stated, "none **[*5]** of [the references cited in the Office Action] alone or in any combination thereof teaches or suggests co-micronization of a mixture of fenofibrate and a solid surfactant, wherein the particles in said co-micronized mixture have mean diameter less than 15 [mu] m." (Id., at P 88).

The amendment also addressed dissolution, stating that it could "be seen in all instances fenofibrate in the co-micronized mixture dissolves about 20-25% faster than fenofibrate that is micronized prior to mixing with micronized solid surfactant." (Def.'s 56.1(a)(3) Statement P 91). Fournier stated that "none of [the cited references] teach or suggest that co-micronizing fenofibrate with a solid surfactant will increase the rate at which fenofibrate dissolves compared to the rate at which micronized fenofibrate mixed with micronized solid surfactant dissolves...." (Id., at P 93).

Following the amendments and above arguments, the PTO allowed all of the claims. (Def.'s 56.1(a)(3) Statement P 96).

Claim 1 of the Curtet Patent states, in its entirety:

> A therapeutic composition, which is presented in the form of gelatin capsules and which is useful especially in the oral treatment of hyperlipidemia **[*6]** and hypocholesterolemia, said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 [mu] m. (Id., at P 23).

Claim 8 of the Curtet Patent, which depends on claim 1, states:

> A method for the manufacture of a therapeutic composition according to claim 1, which comprises:
> (i) intimately mixing and then co-micronizing the fenofibrate and solid surfactant,
> (ii) adding lactose and starch to the mixture obtained,

(iii) converting the whole to granules in the presence of water,
(iv) drying the granules until they contain no more than 1% of water,
(v) grading the granules,
(vi) adding polyvinylpyrrolidone and magnesium stearate, and
(vii) filling gelatin capsules. (Def.'s 56.1(a)(3) Statement P 24).

Claim 10 of the Curtet Patent states:

> A method for improving the bioavailablilty of fenofibrate *in vivo*, which comprises co-micronization of the fenofibrate and a solid surfactant, the said co-micronization being carried out by the micronization of a fenofibrate/solid surfactant mixture until the particle size of the powder obtained is less **[*7]** than 15 [mu] m. (Def.'s 56.1(a)(3) Statement P 26).

The Curtet Patent states a dosage form of one 300 mg fenofibrate gelatin capsule had been proposed. (Def.'s 56.1(a)(3) Statement P 36). The Curtet Patent also states:

> It is known that micronization of an active principle is capable of improving the dissolution of the said active principle in vivo, and hence its bioavailability. It is known that the addition of a surfactant excipient to a formulation of an active principle is capable of improving absorption and consequently the bioavailability of the said active principle. (Id., at P 37; Curtet Patent).

The only "active principle" discussed in the Curtet Patent is fenofibrate. (Id., at P 38).

The Curtet Patent states that it is the "co-micronization of fenofibrate and a solid surfactant (i.e., the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability of the fenofibrate to a significantly greater extent than that which would be achieved either by adding a surfactant [to fenofibrate], or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate **[*8]** and surfactant." (Def.'s 56.1(a)(3) Statement PP 43-44; Curtet Patent).

The Curtet Patent states that the surfactant "will be selected from solid surfactants so that it can be co-micronized with fenofibrate." (Def.'s 56.1(a)(3) Statement P 56). Sodium lauryl sulfate ("SLS") is the only example of a solid surfactant disclosed in the Curtet patent. (Id., at P 58). "The micronization of the fenofibrate and the solid surfactant will be advantageously carried out in an accelerated air-jet mill. " Furthermore, "to obtain a powder which can be formulated into gelatin capsules ... lactose ... may be added to the co-micronizate of fenofibrate and solid surfactant " (Curtet Patent)

The Curtet Patent sets forth "a method for the preparation of a therapeutic composition containing fenofibrate and a solid surfactant is recommended which comprises: (i) intimately mixing and then co-micronizing the fenofibrate and solid surfactant, (ii) adding lactose and starch to the mixture obtained ..." It also provides "Preparative Examples" to aid in understanding the patent and to show that the patent is non-obvious. For example, "Preparation I" states: "The fenofibrate/sodium lauryl-sulfate mixture **[*9]** is co-micronized in an air-jet micronizer to give a powder with a medium particle size of 3 [mu] m. The lactose and the starch are then added to this powder ..." (Def.'s 56.1(a)(3) Statement PP 45-46, 60; Curtet Patent).

In December 1999, Fournier filed for reexamination of the Curtet Patent (Def.'s 56.1(a)(3) Statement P 97) The request for reexamination stated that an article entitled, "Microbroyage et Dissolution", authored by Georges Boullay, raised a substantial new question of the patentability of the claims of the Curtet Patent. (Id., at P 98). The PTO granted reexamination in early 2000. (Id., at P 99)

During the reexamination, Fournier stated, "unlike fenofibrate which exhibits unexpectedly rapid dissolution when co-micronized with surfactant compared with fenofibrate micronized alone, [other fibrates] show no statistically significant increase in dissolution." (Def.'s 56.1(a)(3) Statement P 102). A declaration by Philippe Reginault, one of the inventors, submitted by Fournier, compared "co-micronized fibrates" with "the corresponding fibrate that was first micronized and then mixed with a micronized solid surfactant" (Id., at P 105). In May 2001, the PTO concluded **[*10]** the reexamination proceeding and upheld the patent. (Id., at P 106).

Descriptions of the process steps that Novopharm employs for manufacturing all three dosage forms of its proposed products have been submitted to the FDA in connection with Novopharm's NDA. (Def.'s 56.1(a)(3) Statement P 108). According to Novopharm's process, fenofibrate is first pre-micronized on its own and in the absence of any other ingredient. (Id., at P 109) The pre-micronized fenofibrate is then dry mixed with lactose monohydrate, pregelatinized starch, croscarmellose sodium and crosspovidone. (Id., at P 110).

Separately, for the above dry mixing step, povidone and sodium lauryl-sulfate are dissolved in water to form a granulating solution. (Def.'s 56.1(a)(3) Statement P 111). The granulating solution is then added to the dry fenofibrate mixture. (Id., at P 112). The mixture of the granulating solution and the dry fenofibrate mixture resulting from the previous step is subjected to a wet granulation process involving the addition of more water and thorough mixing. (Id., at P 113).

Following wet granulation, the mixture is dried, weighed, and assessed for "loss on drying". (Def.'s 56.1(a)(3) Statement P **[*11]** 114). The dried, granulated mixture is then dry blended with additional croscarmellose sodium, crosspovidone, and magnesium stearate to produce granules that can pass through a # 16 mesh screen. (Id., at P 115). The granulated mixture is then blended again, weighed, and stored for eventual encapsulation into gelatin capsules (Id., at P 117).

LEGAL STANDARDS

Summary judgment is proper if "the pleadings, depositions, answers to interrogatories, and admissions on file, together with affidavits, if any, show that there is no genuine issue as to any material fact." *Fed. R. Civ. P. 56(c)*; *see also Celotex Corp. v. Catrett, 477 U.S. 317, 322-23, 91 L. Ed. 2d 265, 106 S. Ct. 2548 (1986)*. All the evidence and the reasonable inferences that may be drawn from the evidence are viewed in the light most favorable to the nonmovant. *Miller v. American Family Mutual Ins. Co., 203 F.3d 997, 1003 (7th Cir. 2000)*. Summary judgment may be granted when no "reasonable jury could return a verdict for the nonmoving party." *Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986)*.

A patent infringement analysis consists **[*12]** of two steps. In the first step, the meaning and scope of the patent claims asserted to be infringed are determined. This is commonly referred to as claim construction. The second step entails proving the infringement by comparing the properly construed claims to the device accused of infringing. *Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995)* (*Markman*).

A. Claim Construction

In construing the claims of a patent, the court reviews the extrinsic evidence of record. This evidence includes the claims of the patent, the specifications, and the prosecution history. *See Bell Atlantic Network Serv., Inc. v. Covad Communications Group, Inc., 262 F.3d 1258, 1267 (Fed. Cir. 2001)* (*Covad*).

Generally, all of the terms in a patent claim are given their plain, ordinary, and accustomed meaning to one of ordinary skill in the relevant art. *Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342 (Fed. Cir. 2001)* (*Rexnord*). Unless compelled to do otherwise, a court should give a claim term the full range of its ordinary meaning as understood by one of ordinary skill in the relevant art. *Rexnord, 274 F.3d at 1342*. **[*13]** Dictionaries and technical treatises, while extrinsic evidence, may also be considered along with the intrinsic evidence when determining the ordinary meaning of claimterms. *Covad, 262 F.3d at 1267*.

Once the plain meaning of a disputed claim term is ascertained, the court must examine the written description and any drawings to confirm that the patentee's use of the disputed term is consistent with the meaning given to such term by the court. *Rexnord, 274 F.3d at 1342*. The written description and any drawings are reviewed to determine if the patentee chose to set forth an explicit definition that is different in scope from that of the ordinary meaning. In addition, the court examines the written description and drawings to determine whether the preferred embodiment falls within the scope of a construed claim because a claim construction that would exclude the preferred embodiment 'is rarely, if ever, correct and would require highly persuasive evidentiary support' *Rexnord, 274 F.3d at 1342*, quoting *Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583 (Fed. Cir. 1996)*. Furthermore, the written description and **[*14]** drawings are reviewed to determine whether the patentee disclaimed any subject matter or has otherwise limited the scope of the claims. *Rexnord, 274 F.3d at 1342*.

Lastly, the court reviews the prosecution history because a statement made during the prosecution of a patent may affect the scope of the invention and the meaning of the claims. *Covad, 262 F.3d at 1268*.

B. Infringement

"In order to prove infringement, a patentee must show that every limitation of the claims asserted to be infringed is found in the accused device." *Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1565 (Fed. Cir. 1997)*. As a matter of law, an accused device cannot infringe if even a single limitation is not satisfied. *Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1349 (Fed. Cir. 1998)*.

Infringement is proved either literally or under the doctrine of equivalents. *See Bai v. L & L Wings, Inc., 160 F.3d 1350, 1353 (Fed. Cir. 1998)*. "To establish literal infringement, every limitation set forth in a claim must be found in the accused product, exactly." *Southwall Technologies, Inc. v. Cardinal IG Co., 54 F.3d 1570, 1576 (Fed. Cir. 1995)* **[*15]**

Under the doctrine of equivalents, an accused device infringes only if it possesses all of the limitations of the claim either literally or equivalently. *Tronzo v. Biomet,*

Inc., 156 F.3d 1154, 1160 (Fed. Cir. 1998). The "doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole." *Warner-Jenkinson v. Davis, 520 U.S. 17, 29, 137 L. Ed. 2d 146, 117 S. Ct. 1040 (1997)* (*Davis*). Furthermore, application of the doctrine cannot be used to erase limitations from the claim. *Davis, 520 U.S. at 29.* The differences between the accused device and the claim limitation must be "insubstantial" to possess an equivalent claim limitation. *Desper Prods. v. Qsound Lab., 157 F.3d 1325, 1338.* This analysis generally turns on whether the accused device performs substantially the same function in substantially the same way to achieve substantially the same result. *Alpex Computer Corp. v. Nintendo Co., 102 F.3d 1214, 1222 (1996).*

Another factor affecting the issue of infringement is the doctrine of prosecution history estoppel. The doctrine of prosecution history estoppel prohibits the application of equivalents and precludes a **[*16]** patentee from obtaining coverage under the doctrine of equivalents of subject matter that was relinquished during the prosecution of the patent. *General Elec. Co. v. Nintendo Co., 179 F.3d 1350, 1362 (Fed. Cir. 1999).*

Prosecution history estoppel occurs as a result of arguments made during prosecution of the patent that show a clear and unmistakable surrender of subject matter through amendments made to overcome patentability rejections (*Bayer AG v. Elan Pharmaceutical Research Corp., 212 F.3d 1241, 1251 (Fed. Cir. 2000))* or through unequivocal arguments or assertions made during patent prosecution (*Desper Prods., Inc. v. Qsound Labs, 157 F.3d 1325, 1338 (Fed. Cir. 1998)* and/or reexamination (*Intermatic Inc. v. Lamson & Sessions Co., 273 F.3d 1355, 1366 (Fed. Cir. 2001).* The determination of what subject matter was surrendered is an objective one, measured from the vantage point of what a competitor reasonably would conclude the patentee had relinquished in order to secure the patent. *Augustine Medical, Inc. v. Gaymar Indus., Inc., 181 F.3d 1291, 1299 (Fed. Cir. 1999).*

ISSUES

A. Claim Construction **[*17]**

The parties dispute the construction of the term "co-micronized". Plaintiffs argue that the term should be given its "ordinary meaning" of "micronized with or together". Defendant argues that the term should be construed narrowly to mean that "fenofibrate and a solid surfactant have been micronized together and in the absence of any other excipients".

In essence, the parties do not disagree as to the common meaning of the term "co-micronized". Both parties agree that the common meaning is construed to mean "micronized with or together". This common meaning is supported by the definitions of the parts of the word. "Co-" is defined the same as "con-" -- "a prefix meaning with or together". Dorland's Illustrated Medical Dictionary 368, 389 (29th ed. 2000). "Micronize" is defined as "to reduce to a fine powder; to reduce to particles a micron in diameter". Dorland's Illustrated Medical Dictionary 1112 (29th ed. 2000). Accordingly, the ordinary meaning of the term "co-micronized" would be "to reduce to a fine powder [micronize] with or together".

Defendant argues that the claim language, specification, and prosecution history support a more narrow definition to include that only fenofibrate **[*18]** and a solid surfactant have been micronized together in the absence of any other excipients. Plaintiff argues that Defendant is impermissibly reading a limitation into the claim from the specification.

The term "co-micronize" or a derivative thereof, i.e., co-micronizing, are used in multiple claims, including claims 1, 8, and 10. In each of these claims, a mixture of fenofibrate and a solid surfactant are micronized together. Claim 10 also refers to the micronization of a "fenofibrate/solid surfactant mixture". No other materials or excipients are identified as being part of and of these mixtures.

The term "co-micronize" or its derivatives are also used throughout the specification. For example, the specification states, in pertinent part, that it "has now been discovered that the co-micronization of fenofibrate and a solid surfactant (i.e., the micronization of an intimate mixture of fenofibrate and a solid surfactant) makes it possible to improve the bioavailability ... than that which would be achieved either by adding a surfactant, or by micronizing the fenofibrate on its own, or by intimately mixing the separately micronized fenofibrate and surfactant." Through this language, **[*19]** Plaintiff distinguished its co-micronized mixture of fenofibrate and a solid surfactant from mixtures obtained by adding a surfactant to fenofibrate, or micronizing fenofibrate by itself, and/or mixing separately micronized fenofibrate and surfactant. By distinguishing its co-micronized mixture from these types of mixtures, Plaintiff's co-micronized mixture cannot include such mixtures. *See O.I. Corp. v. Tekmar Co., 115 F.3d 1576, 1581 (Fed. Cir. 1997)* (description that distinguished claim over prior art narrowed construction of disputed term). In all of the examples for preparing the product, fenofibrate and a solid surfactant are the only materials micronized together. After the co-micronization, other excipients are added.

During the prosecution of the Curtet Patent and the subsequent reexamination, Plaintiff repeatedly alleged that prior art did not teach or suggest co-micronization of a mixture of fenofibrate and a solid surfactant. Further-

more, Plaintiff stated that fenofibrate in the co-micronized mixture dissolves faster than fenofibrate dissolves when micronized fenofibrate is mixed with micronized solid surfactants. The prosecution history demonstrates that **[*20]** Plaintiff distinguished its claims, in part, on the fact that fenofibrate and a solid surfactant would be micronized together. In every instance, no other materials are included in this co-micronization. Furthermore, fenofibrate and a solid surfactant are the only materials identified in reference to the "co-micronized mixture".

The above demonstrates that Plaintiff micronizes, together, fenofibrate and a solid surfactant. The claims, description, and prosecution history do not indicate that anything other than fenofibrate and a solid surfactant are micronized. Furthermore, the description and prosecution history indicate that one of the distinguishing elements of this Patent is the co-micronization of a fenofibrate/solid surfactant mixture. No other excipient is identified as part of this mixture.

In light of the above, one skilled in the art reading the claims, description, and prosecution history would conclude that the term "co-micronize" in claims 1 and 10 does not encompass co-microzination of excipients other than fenofibrate and a solid surfactant.

Based on the above, the term "co-micronized" is construed to mean that fenofibrate and a solid surfactant have been micronized **[*21]** together in the absence of other excipients.

Defendant also seeks to limit the construction of the phrase "fenofibrate/solid surfactant mixture" in claim 10 to exclude any other ingredients other than fenofibrate and solid surfactant. Plaintiff does not dispute this construction.

"Mixture" is defined as "a combination of different drugs or ingredients". Dorland's Illustrated Medical Dictionary 1122 (29th ed. 2000). Accordingly, a fenofibrate/solid surfactant mixture would be defined as a combination of fenofibrate and solid surfactant. No other materials are included in the description of the mixture; and the claims, patent description, and prosecution history support the conclusion that no other materials are included in the mixture.

Defendant also seeks to limit the phrase "mixture of particles of fenofibrate and a solid surfactant" to mean a "mixture wholly of fenofibrate and a solid surfactant, to the exclusion of any other excipients". Plaintiff opposes such construction, arguing that the phrase is properly construed to mean "a resultant mixture composed of (but not necessarily wholly of) particles that are composed of (but not necessarily wholly of) fenofibrate and a solid **[*22]** surfactant".

"Of" is defined as "a function word to indicate the material, parts, or elements composing something". Webster's Third New Int'l Dictionary 1565 (3rd ed. 1986).

In a similar claim, the Eastern District Court of New York construed the language 'net supporters made of PFA, FEP or EPE' to mean that the 'net supporters must be made wholly of PFA, FEP or EPE, and cannot include any other fluorocarbon resin...' *Pall Corp. v. PTI Tech. Inc., 259 F.3d 1383, 1390 (Fed. Cir. 2001)* (*Pall*), quoting *Pall Corp. v. PTI Techs., 1999 U.S. Dist. LEXIS 22893,* Nos. CV-97-1134, CV-98-2871 (E.D.N.Y. Dec. 22, 1999). On appeal, the parties did not dispute this claim construction, and the Federal Circuit "agreed with the district court's claim construction requiring the net supporters to be made of 100% of one of the recited ... resins." *Pall, 259 F.3d at 1390*.

In light of the claim language, and the patent description and prosecution history discussed above, the phrase "mixture of particles of fenofibrate and a solid surfactant" means a "mixture of particles wholly of fenofibrate and a solid surfactant".

B. Infringement

1. Literal Infringement

In order to establish **[*23]** literal infringement, Plaintiff must demonstrate that every limitation in a claim is exactly found in the accused device. *Southwall, 54 F.3d at 1576*. As to claim one, the parties do not dispute that fenofibrate and a solid surfactant are not micronized together in the absence of other excipients in Defendant's product. Accordingly, Defendant does not literally infringe either claim 1 or 10 of the Curtet Patent.

2. Doctrine of Equivalents

Defendant first argues that Plaintiff is estopped from asserting the doctrine of equivalents as to claim 1 and 10's co-microzination limitation.

During the prosecution of the Curtet Patent, Plaintiff amended claim 1, changing the original phrase of "the said composition containing fenofibrate and a solid surfactant which have been co-micronized" to state "said composition containing a co-micronized mixture of particles of fenofibrate and a solid surfactant, wherein the mean particle size of said co-micronized mixture is less than 15 [mu] m." Plaintiff distinguished the prior art from the claimed invention, in part, on the ground that prior art did not teach or suggest co-micronization of fenofibrate and a solid surfactant **[*24]** such that the co-micronization resulted in an improvement in bioavailability. Plaintiff further stated that "none of the [cited] references alone or in combination thereof teaches or

suggests ... that co-micronizing said mixture a lower daily dosage may be administered because the bioavailability of fenofibrate is significantly and unexpectedly increased."

These arguments clearly demonstrate that Plaintiff distinguished its invention from prior art because of the increase in bioavailability obtained through co-micronization of fenofibrate and a solid surfactant.

In the Curtet Patent Plaintiff addressed this increase in bioavailability and distinguished its product and process from those achieved by adding a surfactant or by micronizing the fenofibrate on its own or by intimately mixing the separately micronized fenofibrate and surfactant.

During the reexamination of the Curtet Patent, Plaintiff further distinguished co-micronization of fenofibrate and a solid surfactant to fenofibrate that is micronized alone when discussing dissolution rates in order to distinguish the Curtet Patent.

Based on the arguments made during the prosecution of the patent as to increased bioavailability, **[*25]** patent language as to bioavailability, and the arguments made during reexamination, a competitor would reasonably conclude that Plaintiff relinquished a product and process that involved either adding a surfactant by itself or by micronizing the fenofibrate on its own or by intimately mixing the separately micronized fenofibrate and surfactant.

In the instant case, it is undisputed that Defendant pre-micronizes fenofibrate by itself. The above demonstrates that Plaintiff specifically distinguished its co-micronized product and co-micronization process from those obtained from micronizing fenofibrate by itself, as done by Defendant. Accordingly, Plaintiff cannot establish infringement under the doctrine of equivalents for claims 1 or 10. *See Cole v. Kimberly-Clark Corp., 102 F.3d 524, 532 (Fed. Cir. 1997)* (affirming district court's finding that defendant's accused products did not infringe under the doctrine of equivalents based upon the patent's prosecution history during which plaintiff relinquished coverage to obtain its patent); *Builders Concrete, Inc. v. Bremerton Concrete Products Co., 757 F.2d 255, 260 (Fed. Cir. 1985)*

CONCLUSION

For the **[*26]** forgoing reasons, Novopharm's Motion for Summary Judgment of Noninfringement is granted

Dated: March 19, 2002

JOHN W. DARRAH

United States District Judge

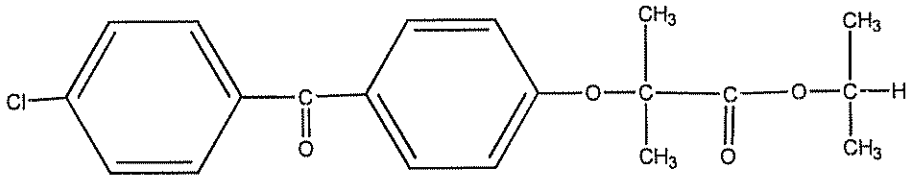
EXHIBIT 2

TRICOR®
(fenofibrate tablets)

R_x Only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 54 mg or 160 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

Inactive Ingredients: Each tablet contains colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, and xanthan gum.

In addition, individual tablets contain:

54 mg tablets: D&C Yellow No. 10, FD&C Yellow No. 6, FD&C Blue No. 2.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of

triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).
The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of 54 mg and 160 mg tablets are equivalent under fed conditions to 67 and 200 mg capsules, respectively.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With fenofibrate tablets, the extent of absorption is increased by approximately 35% under fed as compared to fasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or

metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 160 mg TRICOR per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1
Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort				
Mean baseline lipid values (n=646)	306.9 mg/dL	213.8 mg/dL	52.3 mg/dL	191.0 mg/dL
All FEN (n=361)	-18.7%*	-20.6%*	+11.0%*	-28.9%*
Placebo (n=285)	-0.4%	-2.2%	+0.7%	+7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa)				
Mean baseline lipid values (n=334)	307.7 mg/dL	227.7 mg/dL	58.1 mg/dL	101.7 mg/dL
All FEN (n=193)	-22.4%*	-31.4%*	+9.8%*	-23.5%*
Placebo (n=141)	+0.2%	-2.2%	+2.6%	+11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb)				
Mean baseline lipid values (n=242)	312.8 mg/dL	219.8 mg/dL	46.7 mg/dL	231.9 mg/dL
All FEN (n=126)	-16.8%*	-20.1%*	+14.6%*	-35.9%*
Placebo (n=116)	-3.0%	-6.6%	+2.3%	+0.9%

† Duration of study treatment was 3 to 6 months.
* p = <0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)
The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials[1] of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 160 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2
Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	**Placebo**				**TRICOR**			
Baseline TG levels 350 to 499 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*
Study 2	**Placebo**				**TRICOR**			
Baseline TG levels 500 to 1500 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

* = p<0 05 vs Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

		Lipid Elevation	
Type	**Lipoprotein Elevated**	**Major**	**Minor**
I (rare)	chylomicrons	TG	↑↔C
IIa	LDL	C	-
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	-
IV	VLDL	TG	↑↔C
V (rare)	chylomicrons, VLDL	TG	↑↔

C=cholesterol
TG=triglycerides
LDL=low density lipoprotein
VLDL=very low density lipoprotein
IDL=intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	**LDL Goal (mg/dL)**	**LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)**	**LDL Level at Which to Consider Drug Therapy (mg/dL)**
CHD† or CHD risk equivalents (10-years risk >20%)	<100	≥100	≥130 (100-129:drug optional) ††
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk Factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD = coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 107 mg to 160 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 1.3% in patients receiving dosages equivalent to 107 mg to 160 mg TRICOR per day and was 0% in those receiving dosages equivalent to 54 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR, and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults the concomitant administration of TRICOR and pravastatin resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3a-hydroxy iso-pravastatin when compared to either drug given alone.

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR.

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 160 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take

TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60%

increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

Geriatric Use: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM **Adverse Event**	**Fenofibrate*** **(N=439)**	**Placebo** **(N=365)**
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%

SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 200 mg TRICOR
** Significantly different from Placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.
CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.
DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.
ENDOCRINE SYSTEM: Diabetes mellitus
HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.
METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.
MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.
NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.
RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, pneumonia, laryngitis, and sinusitis.
SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.
SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.
UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, kidney function abnormal, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR. General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should

continue this diet during treatment with TRICOR. TRICOR tablets should be given with meals, thereby optimizing the bioavailability of the medication.

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose of TRICOR is 160 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 54 to 160 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 160 mg per day.

Treatment with TRICOR should be initiated at a dose of 54 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 54 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

TRICOR™ (fenofibrate tablets) is available in two strengths:

54 mg yellow tablets, imprinted with ⊟ and Abbo-Code identification letters "TA", available in bottles of 90 (**NDC** 0074-4009-90).

160 mg white tablets, imprinted with ⊟ and Abbo-Code identification letters "TC", available in bottles of 90 (**NDC** 0074-4013-90).

Storage

Store at controlled room temperature, 15-30°C (59-86°F). Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Laboratoires Fournier, S.A., 21300 Chenôve, France

Made in France

REFERENCES

1. GOLDBERG AC, *et al.* Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics*, 11, pp. 69-83, 1989.
2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., *et al.* (eds.): *The Metabolic Basis of Inherited Disease*, 5th edition, McGraw-Hill, 1983, Chap. 30, pp. 622-642.
3. BROWN WV, *et al.* Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis*. 6, pp. 670-678, 1986.

Revised: NEW

LABORATORIES
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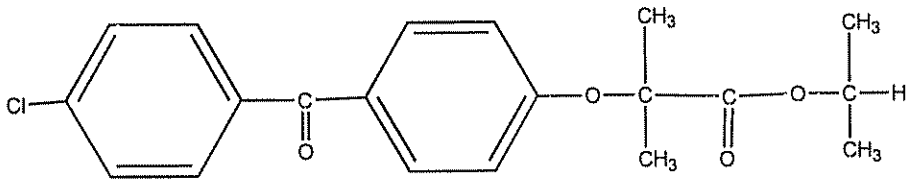
(Nos. 6122, 6123)
NEW

TRICOR® 48 mg and 145 mg
(FENOFIBRATE TABLETS)

R_x Only

DESCRIPTION

TRICOR (fenofibrate tablets), is a lipid regulating agent available as tablets for oral administration. Each tablet contains 48 mg or 145 mg of fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}O_4Cl$ and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.
Inactive Ingredients: Each tablet contains hypromellose 2910 (3cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate.

In addition, individual tablets contain:
48 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D&C Yellow #10 aluminum lake, FD&C Yellow #6 /sunset yellow FCF aluminum lake, FD&C Blue #2 /indigo carmine aluminum lake.
145 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B), an LDL membrane complex, are associated with human atherosclerosis. Similarly, decreased levels of high density lipoprotein cholesterol (HDL-C) and its transport complex, apolipoprotein A (apo AI and apo AII) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C, LDL-C, and triglycerides, and inversely with the level of HDL-C. The independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined.

Fenofibric acid, the active metabolite of fenofibrate, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated

patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.
The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor α (PPARα). Through this mechanism, fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles (which are thought to be atherogenic due to their susceptibility to oxidation), to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly. Activation of PPARα also induces an increase in the synthesis of apoproteins A-I, A-II and HDL-cholesterol.

Fenofibrate also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Absorption

The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration.

Exposure to fenofibric acid in plasma, as measured by C_{max} and AUC, is not significantly different when a single 145 mg dose of fenofibrate is administered under fasting or nonfasting conditions.

Distribution

In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither fenofibrate nor fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

Excretion

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

Special Populations

Geriatrics

In elderly volunteers 77 - 87 years of age, the oral clearance of fenofibric acid following a single oral dose of fenofibrate was 1.2 L/h, which compares to 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

Pediatrics

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

Gender

No pharmacokinetic difference between males and females has been observed for fenofibrate.

Race

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

Renal insufficiency

In a study in patients with severe renal impairment (creatinine clearance < 50 mL/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage. However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 mL/min), the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults (2.1 L/h and 95 L versus 1.1 L/h and 30 L, respectively). Therefore, the dosage of TRICOR should be minimized in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

Hepatic insufficiency

No pharmacokinetic studies have been conducted in patients having hepatic insufficiency.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Concomitant administration of fenofibrate (equivalent to 145mg TRICOR) with pravastatin (40 mg) once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively in 23 healthy adults.

A single dose of pravastatin had no clinically important effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) with atorvastatin (20 mg) once daily for 10 days resulted in approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

Clinical Trials

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Types IIa and IIb)

The effects of fenofibrate at a dose equivalent to 145 mg TRICOR per day were assessed from four randomized, placebo-controlled, double-blind, parallel-group studies including patients with the following mean baseline lipid values: total-C 306.9 mg/dL; LDL-C 213.8 mg/dL; HDL-C 52.3 mg/dL; and triglycerides 191.0 mg/dL. TRICOR therapy lowered LDL-C, Total-C, and the LDL-C/HDL-C ratio. TRICOR therapy also lowered triglycerides and raised HDL-C (see Table 1).

Table 1
Mean Percent Change in Lipid Parameters at End of Treatment†

Treatment Group	Total-C	LDL-C	HDL-C	TG
Pooled Cohort Mean baseline lipid values (n=646) All FEN (n=361) Placebo (n=285)	306.9 mg/dL -18.7%* -0.4%	213.8 mg/dL -20.6%* -2.2%	52.3 mg/dL +11.0%* +0.7%	191.0 mg/dL -28.9%* +7.7%
Baseline LDL-C > 160 mg/dL and TG < 150 mg/dL (Type IIa) Mean baseline lipid values (n=334) All FEN (n=193) Placebo (n=141)	307.7 mg/dL -22.4%* +0.2%	227.7 mg/dL -31.4%* -2.2%	58.1 mg/dL +9.8%* +2.6%	101.7 mg/dL -23.5%* +11.7%
Baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL (Type IIb) Mean baseline lipid values (n=242) All FEN (n=126) Placebo (n=116)	312.8 mg/dL -16.8%* -3.0%	219.8 mg/dL -20.1%* -6.6%	46.7 mg/dL +14.6%* +2.3%	231.9 mg/dL -35.9%* +0.9%

† Duration of study treatment was 3 to 6 months.
* p = <0.05 vs. Placebo

In a subset of the subjects, measurements of apo B were conducted. TRICOR treatment significantly reduced apo B from baseline to endpoint as compared with placebo (-25.1% vs. 2.4%, p<0.0001, n=213 and 143 respectively).

Hypertriglyceridemia (Fredrickson Type IV and V)
The effects of fenofibrate on serum triglycerides were studied in two randomized, double-blind, placebo-controlled clinical trials[1] of 147 hypertriglyceridemic patients (Fredrickson Types IV and V). Patients were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with fenofibrate at dosages equivalent to 145 mg TRICOR per day decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol (see Table 2).

Table 2
Effects of TRICOR in Patients With Fredrickson Type IV/V Hyperlipidemia

Study 1	**Placebo**				**TRICOR**			
Baseline TG levels 350 to 499 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	28	449	450	-0.5	27	432	223	-46.2*
VLDL Triglycerides	19	367	350	2.7	19	350	178	-44.1*
Total Cholesterol	28	255	261	2.8	27	252	227	-9.1*
HDL Cholesterol	28	35	36	4	27	34	40	19.6*
LDL Cholesterol	28	120	129	12	27	128	137	14.5
VLDL Cholesterol	27	99	99	5.8	27	92	46	-44.7*
Study 2	**Placebo**				**TRICOR**			
Baseline TG levels 500 to 1500 mg/dL	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**	**N**	**Baseline (Mean)**	**Endpoint (Mean)**	**% Change (Mean)**
Triglycerides	44	710	750	7.2	48	726	308	-54.5*
VLDL Triglycerides	29	537	571	18.7	33	543	205	-50.6*
Total Cholesterol	44	272	271	0.4	48	261	223	-13.8*
HDL Cholesterol	44	27	28	5.0	48	30	36	22.9*
LDL Cholesterol	42	100	90	-4.2	45	103	131	45.0*
VLDL Cholesterol	42	137	142	11.0	45	126	54	-49.4*

*= p<0 05 vs Placebo

The effect of TRICOR on cardiovascular morbidity and mortality has not been determined.

INDICATIONS AND USAGE

Treatment of Hypercholesterolemia

TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

Treatment of Hypertriglyceridemia

TRICOR is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Markedly elevated levels of serum triglycerides (e.g. > 2,000 mg/dL) may increase the risk of developing pancreatitis. The effect of TRICOR therapy on reducing this risk has not been adequately studied.

Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, thiazide diuretics and beta-blockers, are sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet. (See WARNINGS and PRECAUTIONS).

Fredrickson Classification of Hyperlipoproteinemias

		Lipid Elevation	
Type	**Lipoprotein Elevated**	**Major**	**Minor**
I (rare)	chylomicrons	TG	↑↔C
IIa	LDL	C	-
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C, TG	-
IV	VLDL	TG	↑↔C
V (rare)	chylomicrons, VLDL	TG	↑↔ C

C=cholesterol
TG=triglycerides
LDL=low density lipoprotein
VLDL=very low density lipoprotein
IDL=intermediate density lipoprotein

NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	**LDL Goal (mg/dL)**	**LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)**	**LDL Level at Which to Consider Drug Therapy (mg/dL)**
CHD† or CHD risk equivalents (10-years risk >20%)	<100	≥100	≥130 (100-129:drug optional) ††
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk Factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD = coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still >200 mg/dL, non HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

CONTRAINDICATIONS

TRICOR is contraindicated in patients who exhibit hypersensitivity to fenofibrate.

TRICOR is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

TRICOR is contraindicated in patients with preexisting gallbladder disease (see WARNINGS).

WARNINGS

Liver Function: Fenofibrate at doses equivalent to 96 mg to 145 mg TRICOR per day has been associated with increases in serum transaminases [AST (SGOT) or ALT (SGPT)]. In a pooled analysis of 10 placebo-controlled trials, increases to > 3 times the upper limit of normal occurred in 5.3% of patients taking fenofibrate versus 1.1% of patients treated with placebo.

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. The incidence of increases in transaminases related to fenofibrate therapy appear to be dose related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations to at least three times the upper limit of normal was 13% in patients receiving dosages equivalent to 96 mg to 145 mg TRICOR per day and was 0% in those receiving dosages equivalent to 48 mg or less TRICOR per day, or placebo. Hepatocellular, chronic active and cholestatic hepatitis associated with fenofibrate therapy have been reported after exposures of weeks to several years. In extremely rare cases, cirrhosis has been reported in association with chronic active hepatitis.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with TRICOR , and therapy discontinued if enzyme levels persist above three times the normal limit.

Cholelithiasis: Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. TRICOR therapy should be discontinued if gallstones are found.

Concomitant Oral Anticoagulants: Caution should be exercised when anticoagulants are given in conjunction with TRICOR because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time/INR. The dosage of the anticoagulant should be reduced to maintain the prothrombin time/INR at the desired level to prevent bleeding complications. Frequent prothrombin time/INR determinations are advisable until it has been definitely determined that the prothrombin time/INR has stabilized.

Concomitant HMG-CoA Reductase Inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase),

respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also **CLINICAL PHARMACOLOGY**, Drug-drug interactions).

The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

Mortality: The effect of TRICOR on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established.

Other Considerations: In the Coronary Drug Project, a large study of post myocardial infarction of patients treated for 5 years with clofibrate, there was no difference in mortality seen between the clofibrate group and the placebo group. There was however, a difference in the rate of cholelithiasis and cholecystitis requiring surgery between the two groups (3.0% vs. 1.8%).

Because of chemical, pharmacological, and clinical similarities between TRICOR (fenofibrate tablets), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to TRICOR .

In a study conducted by the World Health Organization (WHO), 5000 subjects without known coronary artery disease were treated with placebo or clofibrate for 5 years and followed for an additional one year. There was a statistically significant, higher age-adjusted all-cause mortality in the clofibrate group compared with the placebo group (5.70% vs. 3.96%, p=<0.01). Excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. This appeared to confirm the higher risk of gallbladder disease seen in clofibrate-treated patients studied in the Coronary Drug Project.

The Helsinki Heart Study was a large (n=4081) study of middle-aged men without a history of coronary artery disease. Subjects received either placebo or gemfibrozil for 5 years, with a 3.5 year open extension afterward. Total mortality was numerically higher in the gemfibrozil randomization group but did not achieve statistical significance (p=0.19, 95% confidence interval for relative risk G:P=.91-1.64). Although cancer deaths trended higher in the gemfibrozil group (p=0.11), cancers (excluding basal cell carcinoma) were diagnosed with equal frequency in both study groups. Due to the limited size of the study, the relative risk of death from any cause was not shown to be different than that seen in the 9 year follow-up data from World Health Organization study (RR=1.29). Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group did not differ statistically from that observed in the WHO study.

A secondary prevention component of the Helsinki Heart Study enrolled middle-aged men excluded from the primary prevention study because of known or suspected coronary heart disease. Subjects received gemfibrozil or placebo for 5 years. Although cardiac deaths trended higher in the gemfibrozil group, this was not statistically significant (hazard ratio 2.2, 95% confidence interval: 0.94-5.05). The rate of gallbladder surgery was not statistically significant between study groups, but did trend higher in the gemfibrozil group, (1.9% vs. 0.3%, p=0.07). There was a statistically significant difference in the number of appendectomies in the gemfibrozil group (6/311 vs. 0/317, p=0.029).

PRECAUTIONS

Initial therapy: Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting TRICOR therapy. Every attempt should be made to control serum lipids

with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

Continued therapy: Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of TRICOR. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 145 mg per day.

Pancreatitis: Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy in patients with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon mediated through biliary tract stone or sludge formation with obstruction of the common bile duct.

Hypersensitivity Reactions: Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with fenofibrate, including rare spontaneous reports of Stevens-Johnson syndrome, and toxic epidermal necrolysis. Urticaria was seen in 1.1 vs. 0%, and rash in 1.4 vs. 0.8% of fenofibrate and placebo patients respectively in controlled trials.

Hematologic Changes: Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of fenofibrate therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of TRICOR administration.

Skeletal muscle: The use of fibrates alone, including TRICOR, may occasionally be associated with myopathy. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatine phosphokinase levels.

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

Drug Interactions

Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN COUMARIN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME/INR AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN TIME/INR DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN TIME/INR HAS STABILIZED.

HMG-CoA reductase inhibitors: The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take TRICOR at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

Cyclosporine: Because cyclosporine can produce nephrotoxicity with decreases in creatinine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of

fibrate drugs including TRICOR, there is a risk that an interaction will lead to deterioration. The benefits and risks of using TRICOR with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD) of 145 mg/day, based on mg/meter^2 of surface area). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinomas was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/meter^2 surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg/day; 2 times the human dose), and Gemfibrozil (250 mg/kg/day; 2 times the human dose) (multiples based on mg/meter^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7, and 3 times the MRHD on the basis of mg/meter^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18-month study at the same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Electron microscopy studies have demonstrated peroxisomal proliferation following fenofibrate administration to the rat. An adequate study to test for peroxisome proliferation in humans has not been done, but changes in peroxisome morphology and numbers have been observed in humans after treatment with other members of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Pregnancy Category C: Safety in pregnant women has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (MRHD) and embryocidal in rabbits when given at 9 times the MRHD (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of approximately 9 times the MRHD of 145mg/day of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at

birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of approximately 10 times the MRHD to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of approximately 7 times the MRHD to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of fenofibrate at 9 to 18 times the MRHD to female rabbits caused abortions in 10% to 25% of dams and death in 7% of fetuses at 18 times the MRHD.

Nursing mothers: Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

GERIATRIC USE: Fenofibric acid is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 2% or more of patients treated with fenofibrate during the double-blind, placebo-controlled trials, regardless of causality, are listed in the table below. Adverse events led to discontinuation of treatment in 5.0% of patients treated with fenofibrate and in 3.0% treated with placebo. Increases in liver function tests were the most frequent events, causing discontinuation of fenofibrate treatment in 1.6% of patients in double-blind trials.

BODY SYSTEM **Adverse Event**	**Fenofibrate*** **(N=439)**	**Placebo** **(N=365)**
BODY AS A WHOLE		
Abdominal Pain	4.6%	4.4%
Back Pain	3.4%	2.5%
Headache	3.2%	2.7%
Asthenia	2.1%	3.0%
Flu Syndrome	2.1%	2.7%
DIGESTIVE		
Liver Function Tests Abnormal	7.5%**	1.4%
Diarrhea	2.3%	4.1%
Nausea	2.3%	1.9%
Constipation	2.1%	1.4%
METABOLIC AND NUTRITIONAL DISORDERS		
SGPT Increased	3.0%	1.6%
Creatine Phosphokinase Increased	3.0%	1.4%
SGOT Increased	3.4% **	0.5%
RESPIRATORY		
Respiratory Disorder	6.2%	5.5%
Rhinitis	2.3%	1.1%

* Dosage equivalent to 145 mg TRICOR
** Significantly different from Placebo

Additional adverse events reported by three or more patients in placebo-controlled trials or reported in other controlled or open trials, regardless of causality are listed below.

BODY AS A WHOLE: Chest pain, pain (unspecified), infection, malaise, allergic reaction, cyst, hernia, fever, photosensitivity reaction, and accidental injury.
CARDIOVASCULAR SYSTEM: Angina pectoris, hypertension, vasodilatation, coronary artery disorder, electrocardiogram abnormal, ventricular extrasystoles, myocardial infarct, peripheral vascular disorder, migraine, varicose vein, cardiovascular disorder, hypotension, palpitation, vascular disorder, arrhythmia, phlebitis, tachycardia, extrasystoles, and atrial fibrillation.
DIGESTIVE SYSTEM: Dyspepsia, flatulence, nausea, increased appetite, gastroenteritis, cholelithiasis, rectal disorder, esophagitis, gastritis, colitis, tooth disorder, vomiting, anorexia, gastrointestinal disorder, duodenal ulcer, nausea and vomiting, peptic ulcer, rectal hemorrhage, liver fatty deposit, cholecystitis, eructation, gamma glutamyl transpeptidase, and diarrhea.
ENDOCRINE SYSTEM: Diabetes mellitus
HEMIC AND LYMPHATIC SYSTEM: Anemia, leukopenia, ecchymosis, eosinophilia, lymphadenopathy, and thrombocytopenia.
METABOLIC AND NUTRITIONAL DISORDERS: Creatinine increased, weight gain, hypoglycemia, gout, weight loss, edema, hyperuricemia, and peripheral edema.
MUSCULOSKELETAL SYSTEM: Myositis, myalgia, arthralgia, arthritis, tenosynovitis, joint disorder, arthrosis, leg cramps, bursitis, and myasthenia.
NERVOUS SYSTEM: Dizziness, insomnia, depression, vertigo, libido decreased, anxiety, paresthesia, dry mouth, hypertonia, nervousness, neuralgia, and somnolence.
RESPIRATORY SYSTEM: Pharyngitis, bronchitis, cough increased, dyspnea, asthma, allergic pulmonary alveolitis, pneumonia, laryngitis, and sinusitis.
SKIN AND APPENDAGES: Rash, pruritus, eczema, herpes zoster, urticaria, acne, sweating, fungal dermatitis, skin disorder, alopecia, contact dermatitis, herpes simplex, maculopapular rash, nail disorder, and skin ulcer.
SPECIAL SENSES: Conjunctivitis, eye disorder, amblyopia, ear pain, otitis media, abnormal vision, cataract specified, and refraction disorder.
UROGENITAL SYSTEM: Urinary frequency, prostatic disorder, dysuria, abnormal kidney function, urolithiasis, gynecomastia, unintended pregnancy, vaginal moniliasis, and cystitis.

OVERDOSAGE

There is no specific treatment for overdose with TRICOR . General supportive care of the patient is indicated, including monitoring of vital signs and observation of clinical status, should an overdose occur. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage; usual precautions should be observed to maintain the airway. Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving TRICOR, and should continue this diet during treatment with TRICOR. TRICOR tablets can be given without regard to meals.

For the treatment of adult patients with Primary Hypercholesterolemia or Mixed Hyperlipidemia, the initial dose of TRICOR is 145 mg per day.

For adult patients with Hypertriglyceridemia, the initial dose is 48 to 145 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 145 mg per day.

Treatment with Tricor should be initiated at a dose of 48 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose. In the elderly, the initial dose should likewise be limited to 48 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of TRICOR if lipid levels fall significantly below the targeted range.

HOW SUPPLIED

Tricor® (fenofibrate tablets) is available in two strengths:

48 mg yellow tablets, imprinted with ◻ and Abbo-Code identification letters "FI", available in bottles of 90 (**NDC** 0074-6122-90).

145 mg white tablets, imprinted with ◻ and Abbo-Code identification letters "FO", available in bottles of 90 (**NDC** 0074-6123-90).

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature].. Keep out of the reach of children. Protect from moisture.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A. by Fournier Laboratories Ireland Limited, Anngrove, Carrigtwohill Co. Cork, Ireland.

REFERENCES

1. GOLDBERG AC, *et al*. Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. *Clinical Therapeutics*, 11, pp. 69-83, 1989.
2. NIKKILA EA. Familial Lipoprotein Lipase Deficiency and Related Disorders of Chylomicron Metabolism. In Stanbury J.B., *et al*. (eds.): *The Metabolic Basis of Inherited Disease*, 5th edition, McGraw-Hill, 1983, Chap. 30, pp. 622-642.
3. BROWN WV, *et al*. Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study In Patients with Type IIA or IIB Hyperlipidemia. *Arteriosclerosis*. 6, pp. 670-678, 1986.

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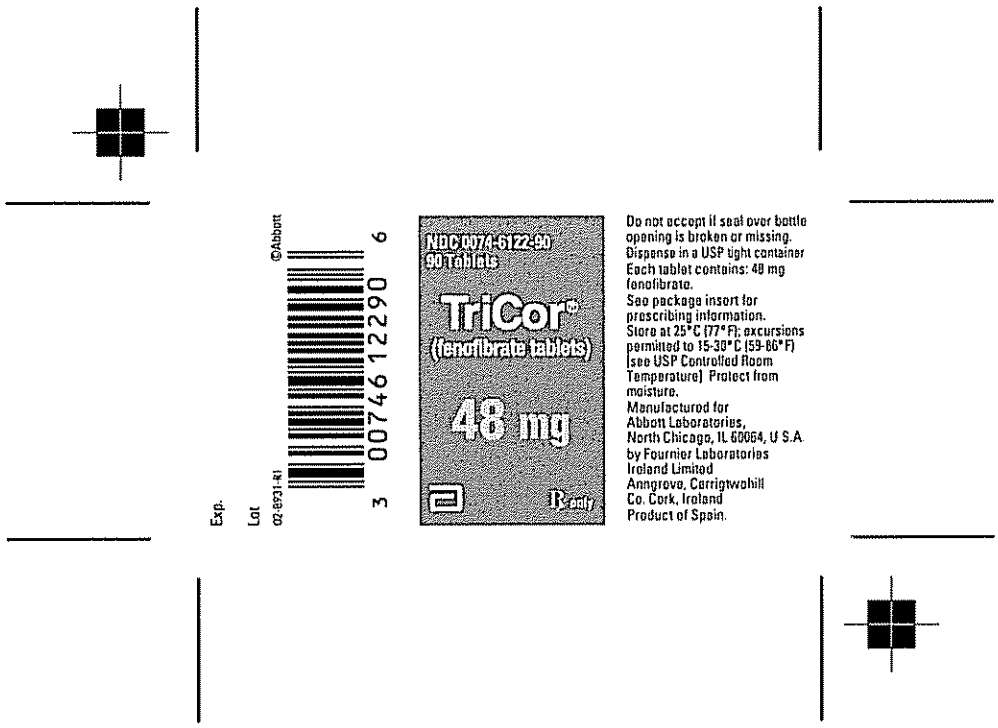
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90 Tablets
TriCor®
(fenofibrate tablets)
48 mg
Rx only
Do not accept if seal over bottle opening is broken or missing.
Dispense in a USP tight container
Each tablet contains: 48 mg fenofibrate.
See package insert for prescribing information.
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